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Synthesis of per-2,3-di-*O*-heptyl-β and γ-cyclodextrins: a new kind of amphiphilic molecules bearing hydrophobic parts

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Abstract—The synthesis of per-2,3-di-*O*-heptyl-β and γ-cyclodextrins, a new kind of amphiphilic cyclodextrins bearing long and stable hydrophobic chains is described. The products are obtained in a three-step synthesis from natural cyclodextrins in good yield. *tert*-Butyldimethylsilyl protection of the primary hydroxyl group was found to be stable under the basic conditions required for the nucleophilic substitution of the bromine derivatives. The structure of the new amphiphilic molecules was proved by NMR spectroscopy and mass spectrometry (ESI-MS or MALDI-TOF-MS).

Cyclodextrins (CDs) are cyclic oligosaccharides obtained during the enzymatic degradation of starch.[1] The most known cyclodextrins consist of six (α-CD), seven (β-CD) or eight (γ-CD) α-(1–4)-D-glucopyranosyl units. These macrocyclic molecules have a truncated cone-shaped structure with the narrower side having primary hydroxyl groups (primary face) and in the large side secondary hydroxyl groups (secondary face). A preformed hydrophobic cavity allows various pharmaceutical applications,[2] mainly the formation of inclusion complexes.[3] Indeed, CDs and their derivatives have been widely used for the solubilization and the transport of biological molecules. The capacity of modified cyclodextrins to form artificial channels has been previously reported[4–6] and a straightforward way to synthesize channels involves molecules having a cavity such as calixarenes,[7] crown ethers[8] or cyclodextrins.[4–6] To be included in lipid bilayer membranes, these molecules must be amphiphilic with a hydrophobic length compatible with the lipid bilayer. Upon adequate chemical modifications, such as persubstitution of one face of the truncated cone by a hydrophobic segment, cyclodextrins can fulfil these conditions and provide transient pores.[6] Indeed, some authors[9,10] have substituted all the hydroxyl groups of the secondary face by ester function to form skirt-shaped cyclodextrins in order to form nanoparticles in water. However, the ester derivatives are subjected to hydrolysis under various conditions encountered for biological applications. A five-step synthetic route to per-6-amino-2,3-di-*O*-hexyl-β-cyclodextrin has been previously reported by Parrot-Lopez et al.[11] and stable Langmuir–Blodgett films were described, demonstrating the high amphiphilic balance of such derivatives. Among the various applications of amphiphilic cyclodextrins,[12] poorly water-soluble drug formulation is attracting a large amount of studies. Recently, gene therapy for muscle transfection was found to be improved by the use of amphiphilic neutral bloc copolymers.[13] We expect the amphiphilic cyclodextrins family to be an alternative to this new transfection area.

Here we will report the synthesis of β- and γ-cyclodextrins derivatives with hydroxyl groups in the primary face and heptyl ether in the secondary side with improved stability whatever the conditions (pH, temperature, etc.). The hydroxyl groups on the primary face requirement is justified by the ability of such compound to initiate cyclic ether polymerization that will be a next step to fit biological membrane thickness.

The per-2,3-di-*O*-heptyl-β,γ-cyclodextrin, amphiphilic CDs derivatives are obtained in a three-step synthesis strategy (Scheme 1).

The hydroxyl groups on the primary face of the CD, the most reactive ones, have to be protected using the

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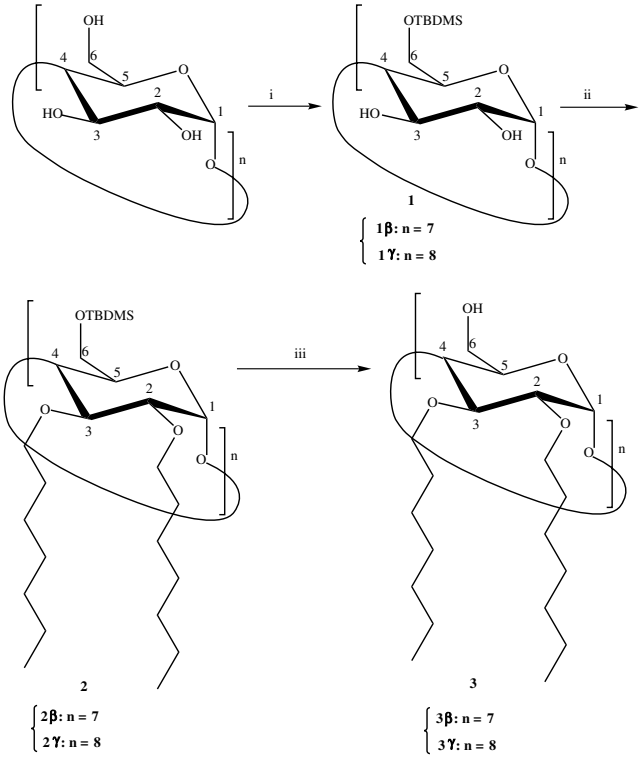

Scheme 1. Synthesis of the per-2,3-di-*O*-heptyl-β,γ-cyclodextrins. Reagents and conditions: (i) TBDMSCl, pyridine; (ii) NaH, heptylbromide, THF/DMF; (iii) TBAF, THF.

Fügedi's method.[14] The protective groups are removed after the complete heptylation of the secondary face of the CD and the final products are obtained with about 60% yield after purifications.

The per-6-*O*-*tert*-butyldimethysilyl-β and γ-cyclodextrins (compounds **1β** and **1γ**) are obtained by protecting the hydroxyl functions in position 6 with *tert*-butyldimethylsilyl groups (TBDMS). The reactions were carried out using the method previously described by Zhang et al.[15] adapted from Fügedi's[14] in which the chromatographic separation is rendered unnecessary by recrystallization from boiling MeOH/$CHCl_3$ (95:5). These reactions lead to yields close to 90% and the structure of the β- and γ-CDs derivatives is proved by NMR and ESI-MS.

The synthesis of per-6-*O*-*tert*-butyldimethysilyl-2,3-di-*O*-heptyl-β and γ-cyclodextrins (**2β** and **2γ**) is achieved in a two-step procedure (Table 1). Sodium hydride (NaH) (73 mmol, 4 equiv per OH function) is added at 0 °C to a solution of (1) in 100 mL of THF/DMF (1/1). The mixture was stirred during a few minutes at 0 °C and then during 20 h at room temperature. Heptylbromide (73 mmol; 4 equiv per OH) was added dropwise and the mixture was stirred for 6 days at room temperature. In a second step, NaH (73 mmol) is added to the reaction mixture, followed by an addition of heptylbromide (73 mmol) 20 h later. After 6 more days, methanol is added to remove the excess of sodium hydride, and the solvents were evaporated under reduced pressure. The residue was dissolved in 100 mL of methylene chloride (CH_2Cl_2) and washed three times with water. A brown oil is obtained after drying over $MgSO_4$, and after filtration and evaporation of the solvent. The final products are obtained after precipitation in methanol.

Table 1. Formation of the CD derivatives **2**

Compound	NaH (equiv)[a]	HeptBr (equiv)[a]	Reaction time (days)	Yield (%)
2β	4	4	14	82
2γ	4	4	14	59

[a] OH equivalent.

Table 2. Formation of the CD derivatives **3**

Compound	TBAF (equiv)[a]	Reaction time (h)	Temperature	Yield (%)
3β	2	72	rt	64
3γ	2	72	rt	60

[a] TBDMS equivalent.

The characterization of those products is realized by ^1H and ^{13}C NMR in $CDCl_3$ and mass spectrometries (MALDI-TOF MS and ESI MS).

Per-2,3-di-*O*-heptyl-β and γ-cyclodextrins (**3β** and **3γ**) are obtained after the removal of the protective group TBDMS. A common synthetic pathway suggests the use of NH_4F as a deprotecting agent.[16,17] This method was found to be ineffective for the deprotection of the per-6-*O*-*tert*-butyldimethysilyl-2,3-di-*O*-heptyl-β and γ-cyclodextrins. Deprotection of the primary hydroxyl functions of **2** was successfully achieved (Table 2) by using tetra-butyl ammonium fluoride (TBAF) as suggested by Lalonde and Chan.[18] TBAF (21 mmol, 2 equiv per TBDMS group) was added to a solution of **2** in THF (100 ml) and the reaction was carried out at room temperature during 72 h. At higher temperature, degradation of the products was observed. The solvent was evaporated and the final product was obtained after an ethyl acetate/water extraction. The derivatives **3** are obtained as white powders after precipitation in methanol. The structures of the final products were characterized by MALDI-TOF MS and homo- and hetero-nuclear NMR spectroscopy[19] (^1H, ^{13}C, ^1H-COSY, ^{13}C-HMQC, ^{13}C-APT).

This letter reports a new amphiphilic cyclodextrins synthesis. The per-2,3-di-*O*-heptyl-cyclodextrins have a long hydrophobic moiety, which imparts water insolubility. The ability of those molecules to form artificial channels will be examined. The presence of the hydroxyl function on the primary face allows the use of such molecules as initiator for subsequent cyclic ether polymerization reactions that will be discussed in a forthcoming publication.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.045.

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